NATION

After the Vancouver Conference, the Big Question

Will New AIDS Drugs Put More People at Risk?

Hyper Mutation!

The AIDS conference featured everything from recommendations on how to prevent HIV among eunuchs in India to pointers on writing a press release. But there was not a single lecture, paper, or symposium on one of the most crucial issues in AIDS today: how to help patients adhere to the highly ballyhooed but dauntingly rigorous "triple-combination therapies."

As reported here two weeks ago, patients must take up to 20 pills a day on a strict schedule, possibly for life. If they miss even a few doses of just one drug, HIV could mutate into a strain that is resistant to all the medications they are taking—and even to some they have never taken.

Again and again, scientists sounded the alarm. And new data revealed that the situation is even worse than previously believed.

For example, HIV can develop resistance not only by mutation—the slow evolution of tiny changes in the virus—but also abruptly, by a kind of viral sex called recombination. If one cell is infected by two viruses—say, one resistant to AZT and another to a protease inhibitor—then they can recombine to form a new virus that is resistant to both drugs. In fact, when researchers tried creating such a mutant virus, it took just one replication cycle to produce it.

Given the risks, doctors are groping for strategies to help patients comply with the arduous regimens. Some physicians are withholding the new therapies from active drug users, for fear they would lose their chance to benefit from the medications even if they get clean and sober. The veterans hospital in San Diego gives counseling with each prescription refill. Boston City Hospital insists patients go through several educational sessions.

The Vancouver conference offered the ideal opportunity for doctors, activists, and patients to share such strategies and develop guidelines. But it never happened. As thousands of patients embark on these rigorous new therapies, that coordination will be sorely missed. —M.S.

BY MARK SCHOOFS

The XI International Conference on AIDS closed last Thursday on an oddly cautious note, given the optimism that prevailed in the press. The media trumpeted the news that new drugs can greatly reduce the amount of HIV in the bloodstream, often to undetectable levels. But scientists kept wondering: When patients have less virus in their blood, are they less able to infect other people? "That's the million-dollar question," says conference cochair Julio Montaner.

No one knows the answer. Despite some dazzling discoveries, researchers still do not understand how HIV infection actually occurs. But what little we do know is fascinating—and sobering.

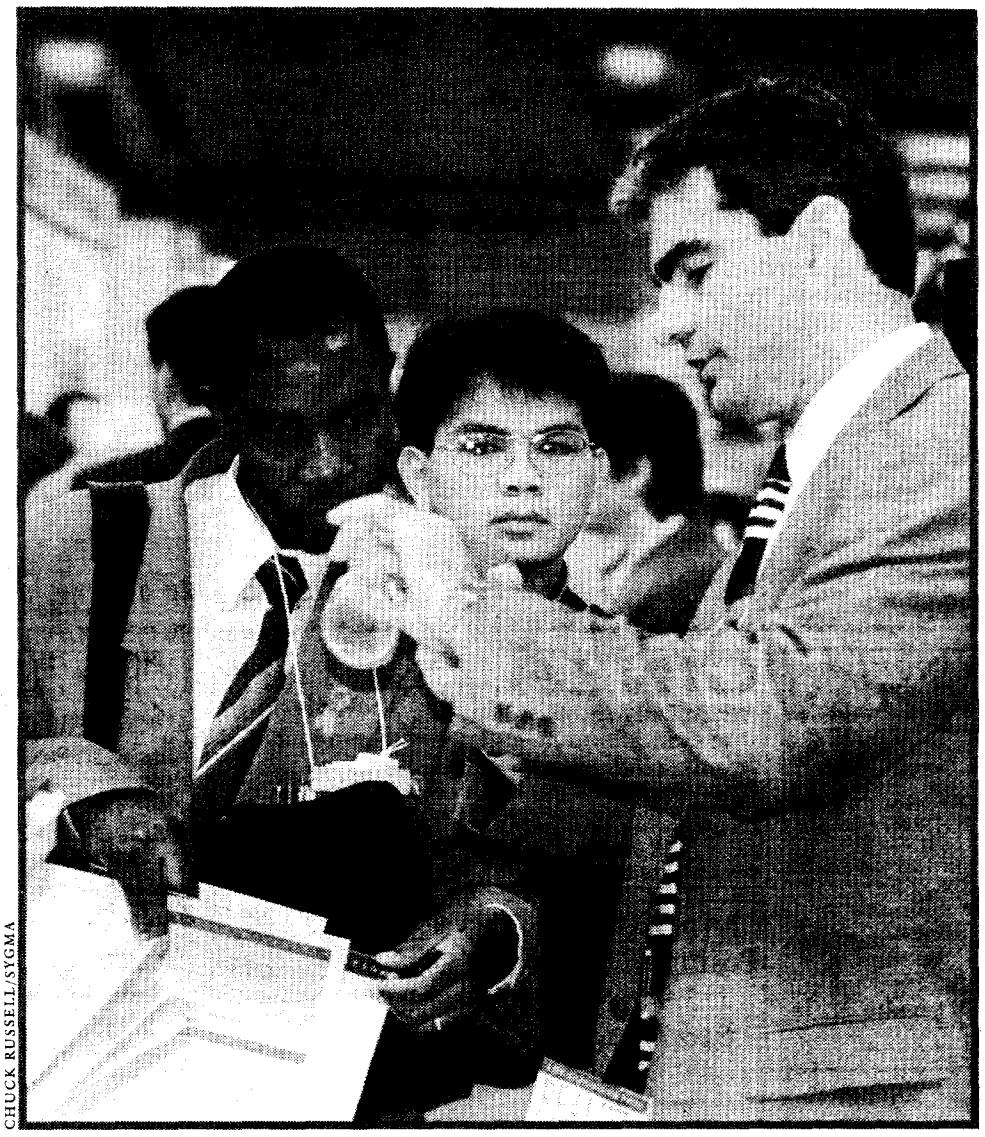
It's common sense to suppose that a patient with less virus in the blood would be less infectious. Myron Cohen, who is studying HIV in semen, explains the reasoning: "A needle stick has a 1-in-250 chance of infecting you, but if you're given a unit of blood in a transfusion, the odds of infection are 90 per cent. What's the difference? The amount of virus." Cohen and others point to studies that show pregnant women with less virus in their blood are less likely to transmit HIV to the fetus.

Clearly, blood is not the only bodily fluid that can transmit HIV. But blood is the only substance routinely tested for the presence of HIV—and what's happening there doesn't necessarily reflect what's happening elsewhere in the body. At the AIDS conference, several studies showed that patients with consistent levels of virus in their blood had hugely varying levels in their semen or vaginal secretions, especially if they had a sexually transmitted disease.

This has led some researchers to wonder whether drugs that work against HIV in the blood will work as effectively in the genital tract. The handful of experiments that have addressed this question suggest that some drugs do suppress virus in genital fluids. But scientists have only recently begun to test the efficacy of protease inhibitors—the drugs that have generated the highest hopes—in semen and vaginal secretions. At the conference, it was noted that different parts of the body can harbor different strains of the virus. One worry is that the genital tract might contain a strain that is easier to transmit. At this point, no one knows.

Perhaps the most crucial question is the most basic: Does HIV cause infection when it is floating free in semen or vaginal fluid? Or, like a Trojan horse, does an infected cell carry the invader into someone else's body? Evidence goes both ways. Test-tube studies show that "cell-associated" HIV is better than free virus at infecting cells lining the human cervix. But when the vaginas of monkeys are swabbed with SIV, the simian cousin of HIV, virus in cells infects much less efficiently than free-floating virus. It's possible that HIV can be transmitted both ways.

The question is important because when the new drugs are administered, they first suppress virus in bodily fluids, along with virus trapped in one type of immune-system cell (called CD4+ T-lymphocytes). But HIV also infects other cells, especially macrophages, which circulate in blood, vaginal fluid, and semen. These cells can harbor the virus even when it is gone from other parts of the body. In a widely discussed presentation at the conference, researcher David Ho estimated that even if the best drugs worked perfectly, it could take up to three years for all infected macrophages to die out.



CHUCK RUSSELL/SYGMA

Delegates to the International AIDS Conference watch a demonstration of the "female condom"—but will they use it?

Partly because of such longevity, every scientist interviewed for this story believes that people with no detectable virus in their blood or seminal plasma can still be infectious. One researcher, who studies HIV in semen, was sure of it. "People in our studies with no detectable virus in their blood or semen have infected other patients in our clinic," said this scientist, who asked not to be named. He conceded that his evidence was only anecdotal, but added, "We have a small clinic. Everyone knows everyone else, so I'm pretty sure it happened."

If the new drug regimens merely reduced infectivity, they could still curtail the epidemic, at least in the developed world. Indeed, researchers such as Cohen envision integrating HIV treatment into prevention efforts. "Our goal is not to say to an individual, 'We've stamped you noninfectious.' " Cohen explains. Instead, he hopes to ascertain "the concentration of HIV that's necessary to infect" on average. Public health authorities could then recommend that patients use drugs to suppress their virus below that level.

Aside from the ethical and legal tangles of such a strategy—would people with AIDS be pressured to take the drugs?—it might also backfire. David Cooper, a veteran HIV researcher, raised this specter in a speech at the conference's closing ceremony. "If infectivity is shown to be lower," he asked, "will this lead to . . . a surge of recidivism in sexual and injection practices?" In that case, less infectivity might be outweighed by more risk taking—and the epidemic could actually spread faster. Moreover, given the likelihood that drug-resistant strains of HIV will develop and spread, new cases of AIDS might be far more difficult to treat.

Why has the good news about new drugs incited such fear? In part, the answer can be found by asking another question: Why, 15 years into the epidemic, do we know so little about how HIV is transmitted?

"I think virologists have been loathe to work with genital secretions," says Harvard researcher Deborah Anderson, who is studying the sexual transmission of HIV. "It wasn't glamorous." She also notes that "funding for reproductive biology dried up, possibly because of the long-term Republican dominance in government."

Better research into HIV transmission might have hastened development of so-called "topical microbicides," creams to protect against sexual transmission of HIV. Gay men and prevention workers in the developing world (where AIDS is spread mainly through heterosexual intercourse) have been clamoring for such a product since the virus was first discovered. But only now—when new drugs have emphasized the enormous costs of ongoing HIV therapy and when HIV has exploded among women in the United States—is the government committing itself to a four-year, $100-million effort to develop such a cream. Many experts believe that it will take even longer to bring this product to market.

In short, the sexual politics that sabotaged so much of the early efforts to combat AIDS linger on, endangering countless lives and threatening our greatest success. ❖